Environmental Health Perspectives
Vol. 26, pp. 151–158, 1978

Autonomic Innervation of the Heart

by E. W. Van Stee*

This brief review describes recent advances in the areas of myocardial receptors that discharge into nonmyelinated, afferent, vagal C-fibers and the regional distribution of sympathetic postganglionic neurons to the myocardium.

Complex, nonencapsulated nerve endings discharging into myelinated afferents have been known to exist for many years. More recently, however, indirect evidence for the existence of cardiac receptors that are either silent or exhibit low resting rates of activity, and discharge into slowly conducting C-type fibers, has been demonstrated. The receptors themselves have not yet been identified histologically. Cardiac receptors include subpopulations that are preferentially activated by chemical stimuli, including a variety of exogenous chemicals as well as prostaglandins. Another subpopulation is preferentially activated by mechanical stresses in the physiological range. Further investigation may reveal their participation in overall cardiovascular regulation, and mediation of responses to exogenous chemical stimuli.

Four principal cardiac sympathetic nerves have been identified in the right thoracic region and three on the left. Most carry sympathetic and parasympathetic fibers. Stimulation of individual nerves, before and after parasympathetic blockade, results in regionally, well-defined myocardial responses.

The purpose of the opening session of the conference is to describe the structural and functional basis for expressions of cardiac toxicity. In order to complement, rather than overlap unnecessarily, the other presentations, I have chosen to limit this discussion to the extrinsic and intrinsic innervation of the heart and its autonomic control, with some comments on reflex regulation.

Toxicity in its broadest sense refers to the harmful or unwanted biological effects of chemicals. Toxicity usually represents dose-dependent responses of organisms to interactions with both clinically useful drugs as well as other chemicals. In some instances, toxicity may be considered to be an extension or exaggeration of a therapeutic action of a drug. For example, one of the clinically useful actions of cardiac glycosides is the slowing of the velocity of atrioventricular conduction. Increasing the drug dosage further slows atrioventricular velocity that may continue to the point of heart block, evidence of toxicity. In other drugs, toxicity may be unrelated to mechanisms of therapeutic action. Disulfiram is an example of this phenomenon. The clinical usefulness of disulfiram in the management of alcoholism is the result of the ability of the drug to inhibit liver aldehyde dehydrogenase. Side effects referable to the autonomic nervous system, on the other hand, may be attributable to the fact that a metabolite of disulfiram also inhibits dopamine-β-hydroxylase (*1*). Finally, toxicity also may be an expression of the biological action of chemicals with no known therapeutic value.

One easily could get into semantic difficulties by scrutinizing such simplified definitions too closely. But the exercise probably would not be worth the effort, since a precise definition of toxicity would not provide any added insight into the mechanisms and consequences of such action.

In order to preserve some sense of order in what can become a very confusing area, the discussion begins with a consideration of thoracic cardiovascular receptors, moves to the afferent limb, thence to the central nervous system, and finally, to the efferent limb.

Many specialized tissues that serve as physiological transducers are located within the cardiovascular system. Areas sensitive to mechanical stress include the carotid sinus and the atriocaval region. Distention of the intrapulmonary vessels elicits reflex responses in the cardiovascular system (*2*), and evidence has been presented supporting a baroreceptor function of the pulmonary artery, pulmonary vein, and the left atrium (*3*). Distension of the aorta also activates baroreceptor reflexes (*4*).

* National Institute of Environmental Health Sciences, P. O. Box 12223, Research Triangle Park, North Carolina 27709.

The carotid and aortic bodies are chemosensitive structures important to cardiovascular regulation. Central nervous system chemoreceptors also play an important role in the regulation of respiration and the circulation, and is a topic reviewed elsewhere (*5*). Other chemoreceptors are located in the subepicardial region and throughout the myocardium of the left ventricle.

Thoren (*6*), in an elegant study, confirmed the existence of a large number of receptors responding to mechanical stress. They were located in the left ventricle and discharged into afferent vagal C fibers (Fig. 1). He mapped a substantial number of these receptors in the open-chested cat heart. They were distributed throughout the left ventricular free wall and the interventricular septum. The resting-firing rate was low but rose with increased left end diastolic pressure, and increases in contractility at constant end diastolic pressure.

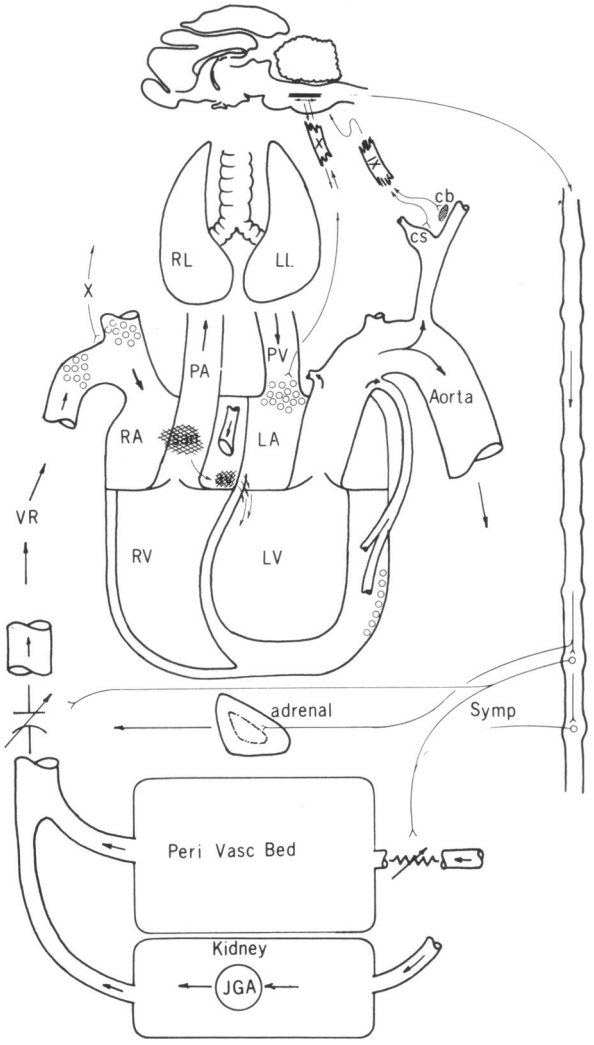

FIGURE 1. Cardiovascular homeostasis is dependent on the integrated functioning of a wide variety of reflexes. Receptors are located throughout the thoracic viscera that discharge into either myelinated or unmyelinated afferents. Most of the afferent impulses are conducted centrally by the glossopharyngeal (IX) or vagus (X) nerves. Some travel with sympathetic fibers. The atriocaval junction and left ventricular myocardium are richly innervated with receptors discharging into nonmyelinated, vagal, C-type fibers.

It is difficult to assess the physiological significance of the results of studies on open-chested animals because of the decidedly unphysiological state of the animal. Transmural pressure, for example, should be a variable important to left heart mechanoreceptor function.

Thames et al. (*7*), in an effort to tidy up this loose end, studied the behavior of the receptors in spontaneously breathing, closed-chested cats. The behavior of atrial receptors differed somewhat from that of the ventricular population. Three of eight atrial receptors, and four of five ventricular receptors were silent under resting conditions. This confirmed the observations of Thoren (*6*) that the spontaneous discharge rate of the ventricular receptors, in particular, was low.

The discharge pattern of the atrial, but not the ventricular, receptors was a function of the respiratory and cardiac cycles. The discharge rate increased during phases of the cardiac cycle characterized by rising wall tension, i.e., end-diastole and early systole. This was further correlated with the respiratory cycle such that the discharge rate increased during end inspiration and early expiration, periods of the greatest thoracic negative pressure. The response of the ventricular receptors to mechanical stress was qualitatively similar to that of the atrial receptors. Interventions tending to increase end diastolic or peak systolic pressures, increased the discharge rate.

As noted by Thames et al. (*7*), a functionally distinct population of cardiac receptors was found in the atrial subendocardium. Stimulation of ventricular receptors caused bradycardia and hypotension, but stimulation of atrial receptors caused an increased heart rate and increased urine flow. Atrial receptors are found in the greatest abundance near the junction of the superior and inferior vena cava with the right atrium (Fig. 1). Certain drugs, e.g., veratrum alkaloids, have been known to elicit cardiovascular depression since the phenomenon was first reported by Bezold in 1867 (*8*). Linden (*9*) has reviewed evidence for the existence of subepicardial ventricular receptors whose stimulation by veratrum activated the afferent limb of what has become known as the Bezold and Jarisch reflex. The response is bradycardia and hypotension.

Thames (*10*), in another study, detected an inhi-

bition of renin release following the intracoronary injection of veratrum. The response was abolished by vagotomy. Dawes (*11*) had demonstrated 30 years earlier that the intracoronary injection of veratrum activated mainly left ventricular receptors. Thus, Thames was able to conclude that chemical activation of left ventricular receptors reflexly inhibited renin release.

Another example of the chemonsensitivity of ventricular receptors was provided by the studies of Sleight et al. (*12*) who elicited reflex hypotension and bradycardia in dogs by the epicardial application of ouabain. The effects were blocked by anesthesia of the epicardium and cooling of the vagi. They further determined that the afferents were of the C-type, and thus the ouabain effects were mediated by the activation of ventricular receptors.

Figure 2 represents an effort to present in concise form the location of some cardiovascular receptors associated with myelinated and nonmyelinated afferent fibers. The nonmyelinated C-type fibers may be distinguished functionally from the myelinated fibers on the basis of conduction velocity (*13*). Nonmyelinated fibers typically conduct at velocities of 2 m/sec or less. Myelinated fibers conduct at varying velocities up to 50 m/sec. The junctions of the superior and inferior vena cava with the right atrium are areas richly innervated with receptors of the C-type (*9*). Some are also found in the aorta and pulmonary vein (*14*). Ventricular receptors, although found in both right and left ventricles, seem to be preferentially distributed to the left (*9*). The left ventricular receptors discharging into vagal afferent C-type fibers are the receptors of the Bezold and Jarisch reflex (*8*).

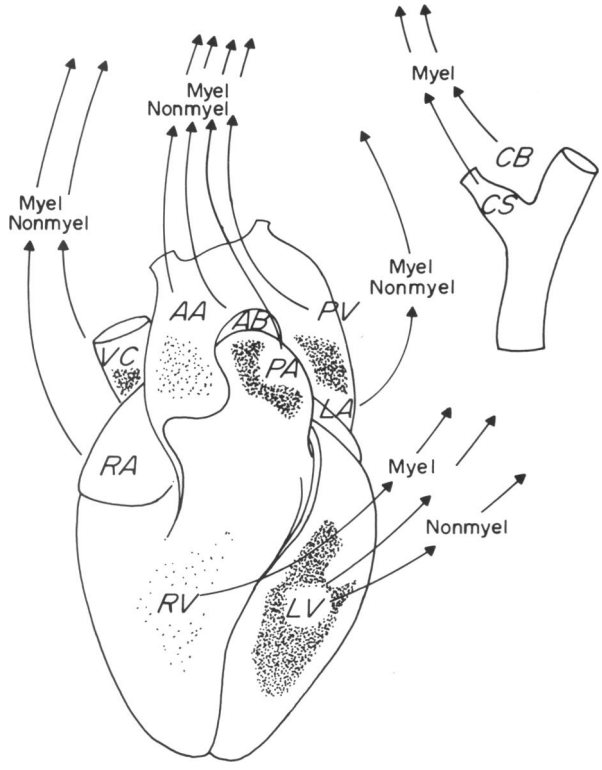

FIGURE 2. Complex, nonencapsulated sensory nerve endings that discharge into myelinated afferent nerve fibers have been known to exist for many years. More recently, however, evidence has been found for the existence of receptors that are silent or have low resting activity. They discharge into slowly conducting, nonmyelinated, vagal C-type fibers (*6*). The stippling represents the areas of the densest innervation (*9*). They are activated by mechanical stress and a variety of chemical stimuli.

Coleridge and Coleridge (*14*) have examined the C-type receptors in the cardiopulmonary system and concluded that they are likely to be found in all thoracic viscera. Furthermore, as suggested in the foregoing discussion, these receptors tend to fall into two groups. One group are mainly mechanoreceptors. The other are mainly chemoreceptors. The Coleridges found that if one selected individual C-type fibers corresponding to a chemosensitive area, the receptors were less sensitive to mechanical stimulation than those selected by mechanical stimulation. The converse was also true.

The Coleridges also cited another observation that may prove to be of physiological significance. Receptors of the chemosensitive type also responded to prostaglandins. Thus, in addition to responding to a variety of exogenous chemical stimuli, the receptors also are activated by substances of physiological significance in the cardiovascular system.

At the highest level, autonomic function is modulated by cortical and subcortical activity. The posterio-lateral nuclei of the hypothalamus are principally sympathetic and their stimulation results in sympathoadrenal discharge (*15*). Preganglionic neurons of the sympathetic division originate in the spinal cord and emerge in the spinal nerves at the levels of T-1 through T-5 (Fig. 3). The preganglionics go, via the white rami, to the cranial and caudal cervical ganglia. Some pass to the stellate ganglia via the ansa subclavia and all of the sympathetic preganglionics synapse with postganglionic neurons in the many sympathetic ganglia (*16*).

The anatomy of the cervicothoracic sympathetic ganglia in the dog differs from that of man. The caudal cervical and anterior thoracic regions are fused in the dog with the result that the structure referred to as the caudal cervical ganglion in man is part of the stellate ganglion in the dog. The caudal cervical ganglion in the dog corresponds to the middle cervical ganglion in man (*17*).

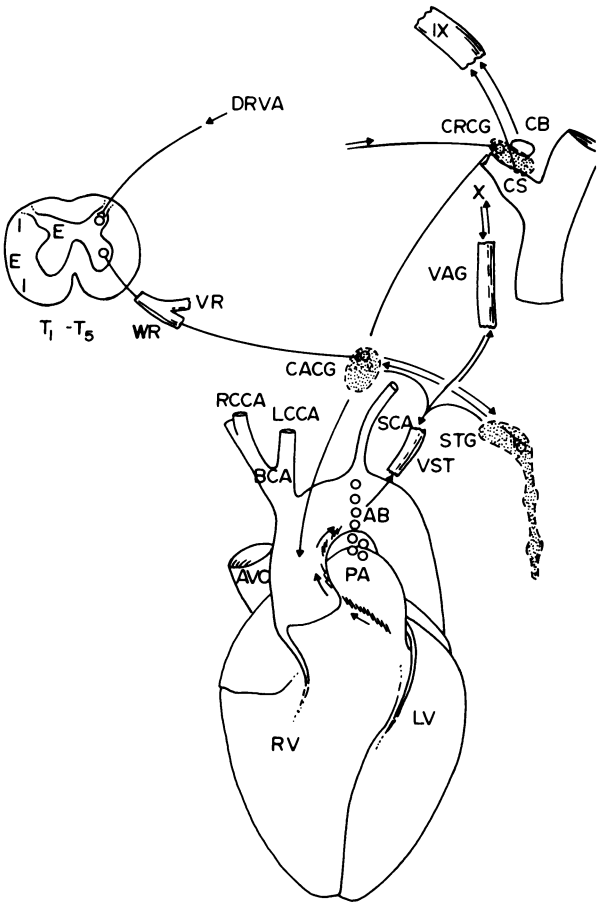

FIGURE 3. The carotid body and carotid sinus discharge into myelinated afferents that are conducted centrally with the glossopharyngeal nerve. The aortic bodies discharge into myelinated afferents that are conducted centrally via the vagus nerve. Preganglionic, sympathetic neurons originate in the spinal cord. They emerge from the cord at T_1–T_5 and synapse with their respective postganglionic neurons in the cervical and stellate ganglia, and the ganglia of the paravertebral, sympathetic chain.

Illert and Gabriel (*18*) have mapped sympathetic pathways in the cervical region of the spinal cord of the cat. Principal sympathetic inhibitory pathways were demonstrated in the ventrolateral columns with minor pathways in the dorsolateral columns. Inhibition of sympathetic activity was shown to take place at the spinal level. Excitatory pathways were demonstrated in the lateral regions of the lateral column and the dorsal columns of the gray matter. The various pathways did not correspond to anatomically clearly defined tracts.

Smith (*19*) studied cardioaccelerator pathways in the dog (Fig. 4). As in other studies, stimulation of the vagosympathetic truck resulted in bradycardia that was converted to tachycardia by atropine. Stimulation of the isolated cervical sympathetic truck resulted in cardiac acceleration that was attenuated by ganglionic blocking agents, suggesting that some of the fibers were preganglionic. Similar results were obtained with stimulation of the dorsal limb of the ansa subclavia. Cardioacceleration from the stimulation of the stellate cardiac nerves, on the other hand, was unaffected by ganglionic blocking agents, suggesting that these fibers were mainly postganglionic.

In the usual classification of fibers, the B-type is typically myelinated and represented by efferent, preganglionic fibers conducting at velocities between 2.5 and 15 m/sec. C-types are nonmyelinated visceral afferents supplying the dorsal roots, referred to earlier. Efferent postganglionic, sympathetic fibers are also C-types. They conduct at velocities of less than 2.5 m/sec Kostreva et al. (*20*) transected the dorsal and ventral roots of the left

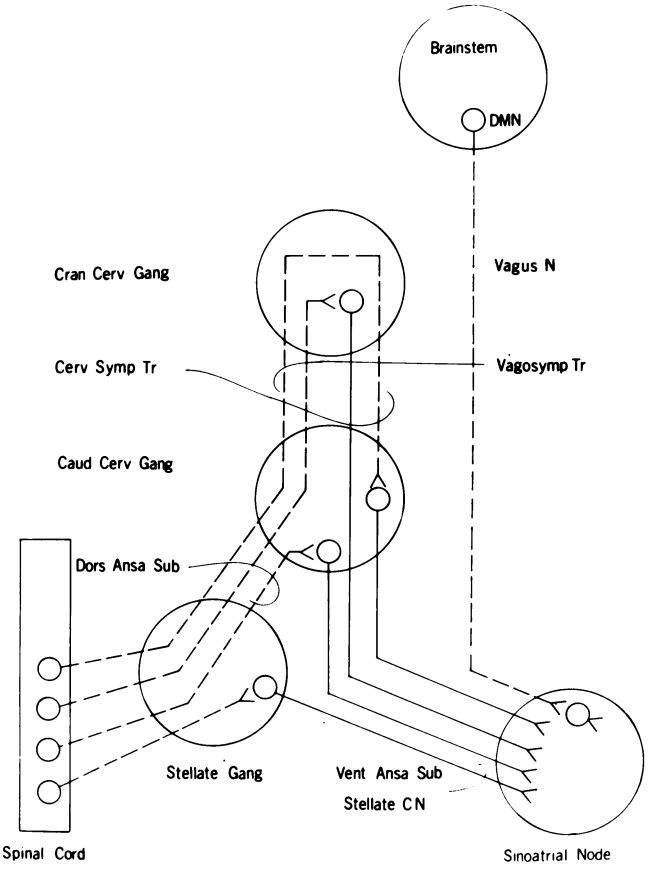

FIGURE 4. Preganglionic, parasympathetic neurons originate in the dorsal motor nucleus of the medulla oblongata. Preganglionic, sympathetic neurons originate in the spinal cord. Functional studies with ganglionic blocking agents confirm that preganglionic (broken lines) and postganglionic (solid lines) fibers are present in the dorsal ansa subclavia and cervical sympathetic trunk. The white rami communicantes consist of preganglionic fibers only, and the stellate cardiac nerves are composed of postganglionic fibers only (*19*).

thoracic nerves in the dog, from T_2 through T_4. They stimulated the distal ends of the ventral roots and recorded evoked potentials from the white rami at T_2, the dorsal ansa subclavia, the vagosympathetic trunk, the ventrolateral and ventromedial cardiac nerves, and the ventral ansa subclavia. They measured conduction velocities as evidence for the presence of the respective fiber types and confirmed the scheme of Smith as far as it went. Smith's scheme should be understood to represent only part of the picture, since the complete picture is considerably more complex than represented in Figure 4. Preganglionics (broken lines) are of the B-type and postganglionics (solid lines) are the C-type. B-fibers were found in the white rami, dorsal ansa, and vagosympathetic trunk. C-fibers were found in the vagosympathetic trunk, ventral ansa, and the cardiac nerves. No C-fibers were found in the white rami.

Randall and co-workers (*21*) have identified the regional distribution of the principal cardiac sympathetic nerves. Figure 5 is a semianatomical schematic diagram of the anterior thoracic region of the dog based on the functional studies performed by that group and the anatomical studies of Mizeres (*22*). Sympathetic nerves to the heart include at least four major groups on the right side and three on the left, not counting the cervical vagosympathetic trunks. The functional distribution of these nerves was determined by electrical stimulation at selected points while monitoring the responses of strain gages strategically placed in the epicardium and endocardium, including papillary muscles. It

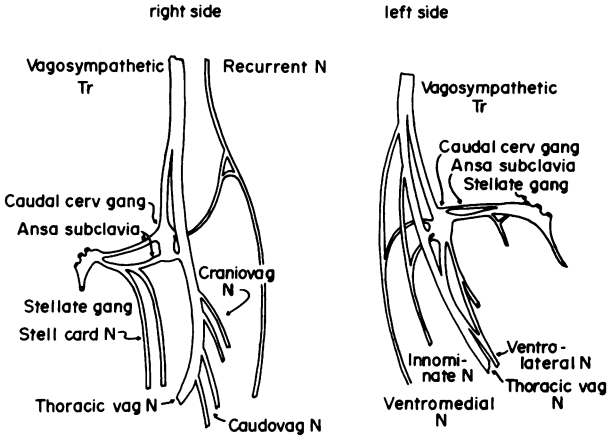

FIGURE 5. The stellate cardiac, craniovagal, caudovagal, and recurrent cardiac nerves are the principal sympathetic nerves to the heart on the right side. The innominate, ventromedial, and ventrolateral nerves are the principal sympathetic cardiac nerves on the left. All of the nerves, except for the stellate cardiac nerves, are mixed, containing both sympathetic and parasympathetic components (*21*).

was concluded that most of the cardiac nerves were composed of both sympathetic and parasympathetic components. The exceptions were the stellate cardiac nerves which were purely sympathetic. The stellate and caudovagal nerves were distributed to the sinoatrial node (SAN) and right atrium. The craniovagal and recurrent cardiac nerves were distributed to the right ventricle.

The cardiac sympathetic nerves on the left were distributed mainly to epicardial surface of the left ventricle and endocardial surfaces of both ventricles. Stimulation of the principal nerves activated different areas of the heart. Stimulation of the vagosympathetic trunk after atropine resulted in widespread activation throughout the heart except for the right atrium.

Norris and Randall (*23*) have classified the principal cardiac nerves into 4 groups based on functional studies in the dog. Type I nerves were defined as those carrying both sympathetic and parasympathetic fibers to all four chambers of the heart. They included the craniovagal, caudovagal, and recurrent nerves on the right side. Type II nerves carried both afferents and efferents, both of which elicited positive inotropic and chronotropic effects when stimulated. The innominate and ventromedial nerves fell into this group. Types III and IV nerves carried only sympathetic efferent fibers. Stimulation of Type III increased both rate and force of contraction. Stimulation of Type IV nerves increased rate preferentially. The ansa subclavia on both sides and the ventrolateral nerve were classified as Type III. The stellates were classified as Type IV.

The major autonomic pathways to the SAN and atrioventricular (AVN) nodes (Fig. 6) were identified by Geis et al. (*24*). As before, most of the nerves stimulated were found to contain both sympathetic and parasympathetic fibers. Most fibers to the general region of the SAN followed pathways that were interrupted by complete transection of the superior vena cava. In all experiments the parasympathetic innervation of the AVN was interrupted by dissection of the superior and inferior margins of the left atrium. Some of the sympathetic innervation of the AVN followed a similar pathway, but interruption of the remainder required complete dissection of the root of the great vessels.

The numbers following the identification of the nerves in Figure 6 refer to the percentage of responses obtained from electrical stimulation of the nerves in the various categories included in the boxes.

Although stimulation of most nerves elicited responses from both general areas, a certain "sidedness" was noted in the sympathetics. Sinoatrial ac-

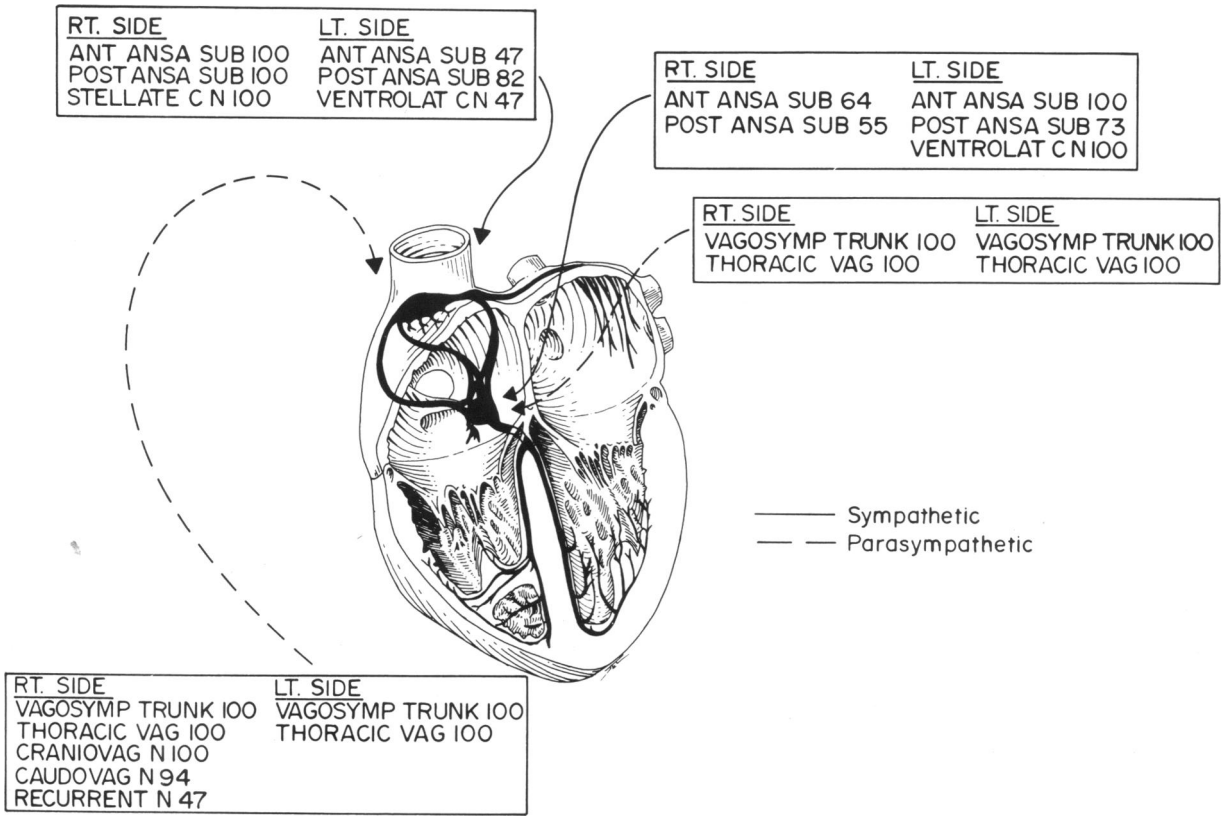

FIGURE 6. Most of the autonomic innervation to the SAN is interrupted by complete transection of the superior vena cava. Parasympathetic innervation to the AVN is interrupted by dissection of the superior and inferior margins of the left atrium, but complete denervation requires dissection of the roots of the great vessels. Numbers following the identification of the cardiac nerves refer to the percentage eliciting autonomic responses from the nodes, when the distal cut ends of the nerves were stimulated electrically (*24*).

tivation was elicited more consistently from stimulation on the right side, and atrioventricular stimulation tended to be associated with the left side. The situation was somewhat different for the parasympathetics. Stimulation of the vagosympathetic trunks and thoracic vagi on both sides slowed both the SAN and AVN in all experiments, but the right craniovagal and caudovagal nerves were distributed predominately to the SAN.

Priola et al. (*25*) have studied the intrinsic innervation in the completely denervated canine heart. The denervated heart is deprived of its postganglionic sympathetic and preganglionic parasympathetic innervation, leaving only the postganglionic parasympathetic neurons (Fig. 7).

The intracoronary injection of small quantities of nicotine (NIC) was accompanied by decreases in rate and force of contraction in unpaced hearts, and decreases in force in paced hearts. The negative inotropic effect of NIC was abolished by D-tubocurarine (dTB) or atropine (ATR).

The intracoronary injection of small quantities of acetylcholine (ACH) elicited responses similar to those of NIC. The responses were blocked by ATR, but not by dTB.

Results from the experiment to this point did not preclude the possibility that NIC was activating postsynaptic nicotinic receptors. What was needed was to be able to block the propagation of the action potential from the neuronal cell body to its terminal arborizations, without interfering with postsynaptic events. Tetrodotoxin (TTX) (*26*) accomplishes this in doses small enough not to interfere appreciably with myocardial cell excitation. The study was completed with the observations that TTX effectively blocked the negative inotropic effect of NIC but not of ACH.

The results of this study supported the conclusion that an intrinsic innervation of the myocardium composed of postganglionic parasympathetic neurons is of functional significance in the canine heart. The negative inotropic response of the denervated heart to small doses of NIC was mediated through the activation of postganglionic receptors

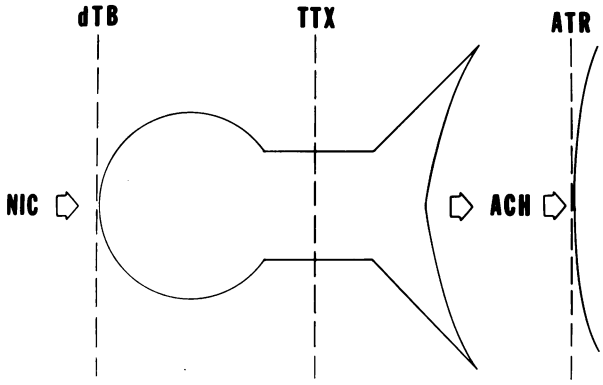

FIGURE 7. Parasympathetic denervation of the heart is followed by degeneration of parasympathetic preganglionic fibers, leaving functional postganglionic neurons intact. Tetrodotoxin (TTX) blocked the propagation of action potentials in the postganglionic neurons following postganglionic receptor depolarization by nicotine (NIC). *d*-Tubocurarine (dTB) blocked the action of NIC at the postganglionic receptor and atropine (ATR) blocked the action of acetylcholine (ACH) at the postsynaptic junction, whether delivered exogenously, or liberated endogenously, in response to postganglionic depolarization (*25*).

leading to the liberation of ACH at the neuroeffector junctions.

Sympathetic denervation of the heart does not result in the depletion of all myocardial catecholamines. Spurgeon et al. (*27*) surgically and chemically denervated the hearts of dogs. The results of their studies were the same for both treatments. The tissues were divided into contractile and conductile myocardium, and assayed for epinephrine (E) and norepinephrine (NE). The average epinephrine content of the conduction system was greater than that of the contractile myocardium in control animals. The NE content, on the other hand, did not follow this pattern. Rather, the SAN and atria had much higher concentrations of NE than the other tissues of the heart.

Sympathectomy by either method resulted in the depletion of NE to very low, but still measurable levels. This was a reflection of the degeneration of sympathetic postganglionics accompanied by the depletion of neural stores of the catecholamine. However, only about one-half of the tissue epinephrine was depleted by sympathectomy.

This was a special significance with reference to the conductile system. Recall that conductile tissue epinephrine concentrations greatly exceeded those of contractile myocardium. The average reduction of epinephrine in the conduction system was down to only 73% of control. The implication from these studies was that substantial quantities of catecholamines, principally epinephrine, were apparently present in the myocardium in nonneural stores, probably in association with chromaffinlike cells that have been described in the heart.

The functional significance of such extraneural stores of myocardial catecholamines remains largely unknown. Pollack (*28*) wrote a provocative article in which he suggested that these catecholamines might serve an obligatory role in pacemaking. He cited evidence that spontaneous pacemaking ceased with the depletion of all residual catecholamines. Pacemaking was restored when catecholamines were replaced.

In conclusion, a number of interesting new findings have emerged in the last 20 years, in the area of the relationship of the autonomic nervous system to the heart. Cardiac receptors that discharge into C-type afferents have been found. They have low or intermittent activity, but respond to mechanical stresses in the physiological range. The implications for their possible participation in the physiological regulation of the heart are made all the more interesting by the observation that certain of the cardiac receptors are sensitive to prostaglandins. That these receptors are activated by a wide variety of exogenous chemicals as well as autacoids has relevance for cardiac toxicology.

The body of work produced by Randall and his co-workers has defined the regional distribution of the sympathetic innervation of the heart, and the door is being opened for the study of the basic mechanisms involved in the maintenance of cardiac rhythmicity.

REFERENCES

1. Goldstein, A., Aronow, L., and Kalman, S. M. Principles of Drug Action, 2nd ed., Wiley, New York, 1974, p. 581.
2. Lloyd, T. C., Jr. Control of systemic vascular resistance by pulmonary and left heart baroreflexes. Am. J. Physiol. 222: 1511 (1972).
3. Lloyd, T. C., Jr., and Friedman, J. J. Effect of a left atrium-pulmonary vein baroreflex on peripheral vascular beds. Am. J. Physiol. 233: H587 (1977).
4. Edis, A. J. Aortic baroreceptor function in the dog. Am. J. Physiol. 221: 1352 (1971).
5. Mitchell, R. A. Location and function of medullary respiratory neurons. Am. Rev. Resp. Dis. 115: 209 (1977).
6. Thoren, P. N. Characteristics of ventricular receptors with nonmedullated vagal afferents in cats. Circ. Res. 40: 415 (1977).
7. Thames, M. D., Donald, D. E., and Shepherd, J. T. Behavior or cardiac receptors with nonmyelinated vagal afferents during spontaneous respiration in cats. Circ. Res. 41: 694 (1977).
8. Bezold, A., and Hirt, L. Über die Physiologischen Wirkungen des Essigsauren. Veratrins. Unters. Physiol. Lab. Würzburg. 1: 75 (1867).
9. Linden, R. J. Function of cardiac receptors. Circulation 48: 463 (1973).
10. Thames, M. D. Reflex suppression of renin release by ventricular receptors with vagal afferents. Am. J. Physiol. 233: H181 (1977).

11. Dawes, G. S. Studies on veratrum alkaloids. J. Pharmacol. Exptl. Therap. 89: 325 (1947).
12. Sleight, P., Lall, A., and Muers, M. Reflex cardiovascular effects of epicardial stimulation by acetylstrophanthidin in dogs. Circ. Res. 25: 705 (1969).
13. Ruch, T. C., and Patton, H. D. Physiology and Biophysics, 19th ed., Saunders, Philadelphia, 1966, p. 81.
14. Coleridge, J. C. G., and Coleridge, H. M. Afferent C-fibers and cardiorespiratory chemoreflexes. Am. Rev. Resp. Dis. 115: 251 (1977).
15. Gebber, G. L., and Klevans, L. R. Central nervous system modulation of cardiovascular reflexes. Fed. Proc. 31: 1245 (1972).
16. Ranson, S. W., and Clark, S. L. The Anatomy of the Nervous System, 10th ed., Saunders, Philadelphia, 1959, p. 150.
17. Miller, M. E. Anatomy of the Dog, Saunders, Philadelphia, 1964, p. 635.
18. Illert, M., and Gabriel, M. Mapping the cord of the spinal cat for sympathetic and blood pressure responses. Brain Res. 23: 274 (1970).
19. Smiuth, D. C. Synaptic sites in sympathetic and vagal cardioaccelerator nerves of the dog. J. Physiol. 218: 1618 (1970).
20. Kostreva, D. R., et al. Ventral root mapping of cardiac nerves in the canine using evoked potentials. J. Physiol. 232: H590 (1977).
21. Randall, W. C., et al. Regional cardiac distribution of sympathetic nerves. Fed. Proc. 31: 1199 (1972).
22. Mizeres, N. M. The anatomy of the autonomic nervous system in the dog. J. Anat. 96: 285 (1955).
23. Norris, J. E., and Randall, W. C. Responses of the canine myocardium to stimulation of thoracic cardiac nerves. Am. J. Physiol. 232: H485 (1977).
24. Geis, W. P., Kaye, M. P., and Randall, W. C. Major autonomic pathways to the atria and S-A and A-V nodes in the canine heart. Am. J. Physiol. 224: 202 (1973).
25. Priola, D. V., Spurgeon, H. A., and Geis, W. P. The intrinsic innervation of the canine heart. Circ. Res. 40: 50 (1977).
26. Narahashi, T. Chemicals as tools in the study of excitable membranes. Physiol. Rev. 54: 813 (1974).
27. Spurgeon, H.A., et al. Catecholamines associated with conductile and contractile myocardium of normal and denervated dog hearts. J. Pharmacol. Exptl. Therap. 190: 466 (1974).
28. Pollack, G. H. Cardiac pacemaking: an obligatory role of catecholamines? Science 196: 731 (1977).